

HOFLAND et al.  
Appl. No. 10/591,847  
Atty. Ref.: 620-454  
Amendment After final Rejection  
November 12, 2009

**REMARKS**

Reconsideration is requested.

Claim 5 has been canceled, without prejudice. Claims 1-4 and 6-10 are pending.

The obviousness-type double patenting rejection of claim 5 over claim 12 of U.S. Patent No. 6,265,385 is moot in view of the above.

Claims 1, 6 and 7 have been revised, without prejudice. Support for the amendments may be found throughout the specification. No new matter has been added.

To the extent not obviated by the above, the Section 103 rejection of claims 1-4 and 6-10 over Jensen (WO 97/25044) and Palepu (U.S. Patent No. 4,963,551), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to believe that Jensen teaches the use of a topoisomerase II poison and a bis-dioxypiperazine and that Palepu teaches that a specific bis-dioxypiperazine ICRF-187 is a cardio-protective agent used in antitumour therapy which also acts as a sensitiser to ionising radiation. The Examiner states that the use of ionising radiation in the treatment of cancer is well known. The Examiner accordingly is understood to believe that the ordinarily skilled person would have considered it obvious to have combined topoisomerase II poison, bis-dioxypiperazine and ionising radiation, and that the "maximum beneficial effect" of such would have allegedly been achieved because Palepu et al teaches that ICRF-187 is a sensitiser to ionising radiation.

The Examiner is urged to appreciate, however, that in the present application the cells exposed to radiation therapy have had no exposure to the bis-dioxypiperazine. Accordingly, there could not have been sensitisation of those cells to radiation therapy. The bis-dioxypiperazine is a hydrophilic compound and has poor blood brain barrier penetration and therefore cannot sensitise brain cells to ionising radiation. This would be known to the ordinarily skilled person at the time of filing of the present application.

The present application demonstrates in Figure 2B, for example, that the combination of the bis-dioxypiperazine dexrozoxane with radiotherapy produced substantially the same results in terms of clonogenic survival as the use of radiotherapy alone. These data are believed to demonstrate that the bis-dioxypiperazine does not sensitise the brain cells to the ionising radiation.

From this information it is apparent that at the time of filing of the present application the ordinarily skilled person would not have been led to believe that the bis-dioxypiperazine in the combination of Jensen would have sensitised the brain to treatment with ionising radiation and thus cause the attainment of the "maximum beneficial effect", as suggested by the Examiner.

Accordingly, it is all the more surprising that, in the method of the present invention, the synergism in the activity of the bis-dioxypiperazine and topoisomerase II poison could be so strongly enhanced when used together with whole brain radiation therapy.

At the time of filing of the present application there was no teaching or suggestion that there could be a synergistic effect obtained with the use of a bis-dioxypiperazine and topoisomerase II poison and whole brain radiation therapy. In fact,

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given that at the time of filing of the present application the skilled person would have known that bis-dioxypiperazines are hydrophilic and would therefore be unable to cross the blood brain barrier, the ordinarily skilled person would have expected that there would have been no sensitisation of the brain cells to radiation therapy and therefore nothing to be gained by using a combination of a bis-dioxypiperazine and topoisomerase II poison with brain radiation therapy. Contrary to the Examiner's belief therefore, the ordinarily skilled person would not have had a reasonable expectation of success. Nothing in the prior art could have led the ordinarily skilled person to predict the surprising results described in the present application.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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